Amendments to the Specification

Please replace the paragraph at page 10, lines 27-32, with the following amended paragraph:

Figs. 8A and 8B show athymic Ncr nude mice injected subcutaneously with chilled ~~Matrigel®~~ MATRIGEL® containing bFGF which resulted in formation of a visible "plug". The plug was photographed four days post implantation. Figs. 8C and 8D are similar to 8A and 8B except that the plug contained HK_a. The arrows in the figures point to the plug periphery. Plug vascularization is visible in Figs. 8A and 8B, but absent in Figs. 8C and 8D.

Please replace the paragraph at page 11, lines 28-31, with the following amended paragraph:

Furthermore, as shown herein, HK_a is effective in an *in vivo* model of angiogenesis. HK_a inhibits the ingrowth of new blood vessels into a reconstituted extracellular matrix ~~(Matrigel)~~ (MATRIGEL®) containing the pro-angiogenic growth factor bFGF implanted subcutaneously into mice.

Please replace the paragraph at page 15, line 31 – page 16, line 11, with the following amended paragraph:

The ability of HK_a to inhibit the proliferation of endothelial cells cultured on different extracellular matrix (ECM) proteins was determined. HK_a (10nM) potently inhibited the proliferation of HUVEC cultured on gelatin, laminin and ~~Matrigel~~ MATRIGEL®, though slightly less potent inhibition, largely overcome by high concentrations of HK_a (50 nM), occurred when cell were cultured on fibronectin or vitronectin. Intermediate effects were observed when cells were cultured on fibrinogen, though cells cultured on collagen types I or IV were resistant to the antiproliferative activity of HK_a. In keeping with the results of proliferation assays, HK_a caused apoptosis

of endothelial cells cultured on gelatin, but not on collagen, and of cells cultured at low density, but not under confluent or near-confluent conditions. Without wishing to be bound by any theory, it appears that mature endothelial cells residing on an intact, collagen-rich basement membrane may be protected from HK_a-induced apoptosis, and that HK_a might selectively target angiogenic endothelial cells in a protease-rich tumor milieu in which ECM is partially degraded.

Please replace the paragraph at page 22, lines 3-11, with the following amended paragraph:

In other experiments, the ability of HK_a to inhibit the proliferation of endothelial cells cultured on different extracellular matrix (ECM) proteins. HK_a (10nM) potently inhibited the proliferation of HUVEC cultured on gelatin, laminin and ~~Matrigel~~ MATRIGEL®, though slightly less potent inhibition, largely overcome by high concentrations of HK_a (50 nM), occurred when cells were cultured on fibronectin or vitronectin. Intermediate effects were observed when cells were cultured on fibrinogen, though cells cultured on collagen types I or IV were resistant to the antiproliferative activity of HK_a.

Please replace the paragraph at page 24, lines 1-16, with the following amended paragraph:

A. Experimental

The effect of HK_a on cytokine-stimulated angiogenesis *in vivo* was determined using a previously-described assay in which the neovascularization of a ~~Matrigel~~ MATRIGEL® "plug" containing bFGF is assessed (Passaniti *et al., Lab Invest* 67:519-528, 1992). Briefly, athymic Ncr nude mice (7-8 weeks old, females) were injected subcutaneously on the left and right mid-back with 0.25 ml of chilled ~~Matrigel~~ MATRIGEL® containing 400 ng bFGF and 50 μg heparin, to which either 25 μl of PBS (left mid-back injection) or an equal volume of PBS containing 0.4 mg/ml HK_a (right mid-

back injection) had been added. Immediately after injection, the ~~Matrigel~~ MATRIGEL® solidified and remained as a solid, subcutaneous "plug" through the 4 day duration of the experiment. At this point, mice were sacrificed, and the skin incised along the mid back and peeled back over the flanks to expose the ~~Matrigel~~ MATRIGEL® plugs. Plugs were then photographed prior to their excision, fixation and processing, as previously described (Passaniti *et al., Lab Invest* 67:519-528, 1992).

Please replace the paragraph at page 24, line 31 – page 25, line 9, with the following amended paragraph:

B. Results

As depicted in Figures 8A and 8B, ~~Matrigel~~ MATRIGEL® plugs containing bFGF induced exuberant vessel ingrowth within 4 days after implantation. In contrast, no neovascularization of ~~Matrigel~~ MATRIGEL® plugs which contained bFGF and HK_a was observed (Figures 8C and 8D). In addition, these plugs remained transparent, as opposed to the opaque appearance acquired by the plugs, suggesting that HK_a blocked the intravasation of migratory cells into the ~~Matrigel~~ MATRIGEL®. The latter hypothesis was confirmed by histological analysis, which demonstrated markedly fewer cells within the HK_a-containing ~~Matrigel~~ MATRIGEL® plugs. Furthermore, the cells which had migrated into these plugs appeared rounded and apoptotic, in contrast to the elongated, migratory phenotype of the cells invading the control plugs.